

Appl. No. : 09/833,030  
Filed : April 10, 2001

### REMARKS

Claim 2 has been amended. New Claim 13 has been added. Thus, claims 2 to 10, and 13 are presented for examination. Specific support for the amendment to claim 2 is discussed below. Support for the new claim 13 can be found in the Specification as filed (page 8, lines 3-4, page 14, line 1). The following remarks address the substance of the Office Action:

**I. Rejection of Claims 2-10 Under 35 U.S.C. §103 over Barner *et al.* in view of Weetall or Sundberg *et al.***

The Examiner has rejected claims 2-10 under 35 U.S.C. § 103(a) over Barner *et al.* (USP 5,986,066) in view of Weetall or Sundberg *et al.* The Examiner asserts that Barner *et al.* teaches a method of oxidizing an olefin on a solid surface with permanganate and periodate to form a functional group for immobilizing a protein, and that combined with the disclosure of an aldehyde functional group from Weetall or Sundberg *et al.* Barner *et al.* renders the claimed invention obvious. Applicants respectfully maintain that the cited references do not render the claimed invention obvious.

The present invention involves oxidizing olefinic groups present on the surface of a solid support to form an aldehyde on the surface of the support and coupling a capture molecule to the aldehyde groups as recited in Claim 2. The Examiner points to Barner *et al.*, who discloses oxidizing octenyl trichlorosilane with permanganate and periodate to form carboxylic groups (*see* col. 8, lines 36-58). The Examiner further referred to Fox *et al.* to support his argument that the presence of an aldehyde on the sensor surface of Barner *et al.* is an inherent result of the oxidation of an olefin to carboxylic acid as described by Barner.

Applicant maintains that the process of Barner produces an aldehyde only as a transient intermediate in a reaction which produces a carboxylic acid as an end product. In fact, the Fox *et al.* reference noted by the Examiner states that aldehyde that is formed during oxidative degradation with hot potassium permanganate is further oxidized to an acid by permanganate, thus indicating that aldehyde presence in the reaction mixture as an intermediate product of the reaction is unstable and temporary. It is well known in the art that the oxidative effects of potassium permanganate can be increased by either raising its temperature or its concentration. The high concentrations of potassium permanganate (2.5 mM) together with high concentration of sodium periodate (100 mM) in Barner *et al.* would also cause the presence of the aldehyde in

the reaction mixture to be transitory. Thus, Barner *et al.*, in fact, teaches away from the invention as claimed in Claim 2, where the formation of the aldehyde functions is the end product of the mild oxidation of olefinic groups by 0.5 nM potassium permanganate and 20 mM sodium periodate (page 9, line 14 of the Specification as filed).

Furthermore, in contrast to the claimed methods in which the capture molecules are bound to the aldehyde functions, in the methods of Barner the carboxylic acid is converted into an N-hydroxysuccinimide ester in the presence of pyridine and the biological molecules are attached to the ester. Thus, there is no suggestion in Barner of attaching capture molecules to an aldehyde group.

In addition, as attested in the accompanying Declaration, N-hydroxysuccinimide is unstable and hydrolyses quickly, rendering it unsuitable for use in microarray fabrication procedures which are optimally conducted using supports having stable reactive moieties.

Weetall and Sundberg relate to methods in which biological molecules are joined to polymerized glutaraldehyde. Because the procedure disclosed in Barner provides a reactive group which can be joined to biological molecules (i.e. the N-hydroxysuccinimide esters), one skilled in the art would have no motivation to add the polymerized glutaraldehyde of Weetall and Sundberg to the methods of Barner. Thus, there would have been no motivation to combine the method of Barner *et al.* with Weetall or Sundberg *et al.*

Furthermore, as attested in the accompanying Declaration, the methods of Weetall and Sundberg, which utilize doubly reactive glutaraldehyde, results in the two reactive groups binding to the surface of the array, rendering them unavailable for binding to a capture molecule. This reduces the density of biological molecules which can be fixed to the support, resulting in reduced sensitivity relative to arrays produced by the claimed methods.

The Examiner also asserted that "since applicant has not disclosed that the aldehyde functional group solves any stated problem or is for any particular purpose, it appears that the invention would perform equally well with either an aldehyde or a carboxylic acid as a functional group".

As discussed below and in the accompanying Declaration, it is not the use of an aldehyde group per se that provides the benefits of the present invention since the methods of Weetall and Sundberg also employ aldehydes. Rather, the present methods generate a greater density of

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aldehyde groups per unit area than the cited methods and provide arrays that are sensitive, reproducible and amenable to automated production.

II. The declaration under 37 C.F.R. 1.132 filed 9/13/02

The Examiner indicated that the declaration under 37 C.F.R. 1.132 filed 9/13/02 is allegedly insufficient to overcome the rejection of Claims 2-10 based upon Barner *et al.* in view of either Weetall or Sundberg *et al.* applied as under 35 U.S.C. §103(a), because in view of the Examiner it refers only to the system described in the above-referenced application and not to the individual claims of the application. In particular, the Examiner asserted that the Declaration was insufficient because it did not show how the method steps of the claimed invention are not obvious over the prior art.

As noted in the Declaration submitted Sept. 9, 2002 (see page 1, paragraphs 4 and 5) a spotting solution of 400 nM on microarrays prepared by the claimed method (specifically, step (a) of the Claim 2) yielded the same signal as a 2000 nM solution on the commercially available product (Telechem, Inc.), also known to have aldehyde functions on its surface.

As demonstrated in Example 3 of the application and further attested in the accompanying Declaration, the claimed methods of generating aldehydes and fixing capture molecules thereto allows a greater a density of aldehyde groups to be obtained in a given area, which in turn allows a greater amount of capture molecules to be affixed within that area and increases the sensitivity of the arrays. Furthermore, as attested in the accompanying Declaration, the arrays produced using the claimed methods have significant uniformity within a single array and little variability from one array to another. Finally, the methods of the present invention are compatible with automated methods for array manufacturing. Each of these advantages is a direct result of the methods used to prepare the array. Accordingly, Applicants maintain that the claimed methods are patentable over the cited references.

In conclusion the Applicants assert that the present invention is not taught or suggested by the Barner *et al.* in view of Weetall or Sundberg *et al.*, as Barner *et al.* clearly teaches away from the invention as claimed.

In view of the foregoing, Applicants respectfully request withdrawal of the rejection to the claims under 35 U.S.C. § 103(a).

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### III. Conclusion

Claim 13 has been added. No new matter has been added herewith.

In view of the foregoing, Applicants respectfully submit the present application is fully in condition for allowance. If any issues remain that may be addressed by a phone conversation, the Examiner is invited to contact the undersigned at the phone number listed below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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Dated: May 27, 2003

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